

THE ACTION OF SOME DIURETICS

BY

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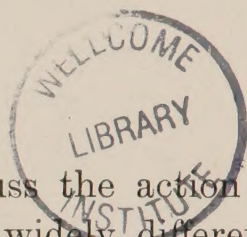


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The Action of some Diuretics.

By H. H. DALE, M.D., and P. P. LAIDLAW, B.C.



OUR object in this communication is to discuss the action of two substances which, in very different ways and in widely different connexions, have been described as specific diuretics, and both of which have recently been the subject of experiment by us in the laboratory.¹ It may seem almost paradoxical to deal thus in a single paper with the action of the drug known as Apocynum and that of the posterior lobe of the pituitary body. We hope to show some justification for this association.

The drug known to the United States pharmacopœia as Apocynum has undergone various vicissitudes of enthusiastic recommendation, and almost equally enthusiastic disparagement. This, we imagine, is no uncommon history for a drug, which usually finds its proper level of appreciation at a point remote alike from those assigned to it by its earliest advocates and adversaries. The earliest claim which we have discovered for the introduction of this drug into civilized medicine is put forward on behalf of a certain Judge Gray, of Chautauqua county, who in 1820 learned from a tribe of Indians the medicinal virtues of the rhizome of *Apocynum cannabinum* in dropsy, and acquired a local reputation for the treatment of such conditions, handing down his information to two generations of medical descendants. The earliest descriptions of its use in medical literature are those of Knapp and Griscom, in 1826 and 1833 respectively. These observers subjected the drug to a laborious chemical examination, which, however, as might be expected from the state of organic chemistry in their day, was barren of result. These earlier observers mention diuresis as an effect of the drug, but their attention seems to have been drawn more particularly to its emetic, cathartic, and diaphoretic actions. Though the use of the drug seems to have spread in the United States, through the middle portion of last century,

¹ For details of the observations discussed and references to the papers cited, see Dale and Laidlaw, *Heart*, Lond., 1909, i, p. 138; and Dale, *Biochem. Journ.*, Liverpool, 1909, iv, p. 427.

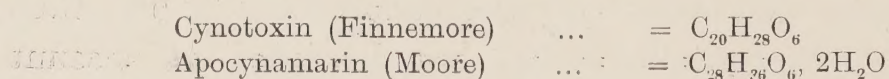
chiefly as a remedy for dropsy, great uncertainty seems to have prevailed as to the nature of its action. An Eclectic Dispensatory of 1855 recommends it in dropsy on account of its diuretic and hydragogue cathartic action: the latter action is emphasized in several publications as the basis of its remedial effect in ascites, while its emetic action in large doses is frequently mentioned. The accounts of this period leave the reader merely with a general impression that the drug probably contains a principle belonging to the group of the drastic purgatives. In 1876 a pharmacological examination by Husemann showed that it has the action of a cardiac tonic of the digitalis group. In 1883 a chemical and pharmacological examination was carried out in Schmiedeberg's laboratory and two preparations obtained—one soluble in alcohol, almost insoluble in water, to which the name Apocynin was given; the other a water-soluble, saponin-like body which was named Apocynein. Of these the former, apocynin, was especially toxic, producing systolic arrest of the frog's heart in very small doses. Unfortunately, neither of these products of Schmiedeberg was crystalline or had any of the characteristics of a pure substance. This has indirectly been a factor in the discredit of apocynum, since the manufacturers, working on a large scale, have been preparing what is doubtless a highly purified version of Schmiedeberg's active principle, and selling, as apocynin, a beautifully crystalline substance practically devoid of activity of any kind. Murray, in 1889, reported the beneficial action of the tincture of apocynum in cases of cardiac dropsy, the pulse being regularized and reduced in rate, the volume of urine increased. It is noteworthy that he used it with success in cases in which digitalis had to be abandoned on account of its emetic action. Murray quotes unpublished pharmacological experiments by Rose Bradford, who found that the tincture of apocynum acted almost entirely on the heart, the beat of which was strengthened, but was simultaneously so reduced in rate by vagus inhibition that the blood-pressure did not rise. According to Bradford the drug had practically no vaso-constrictor action. A year previously, however, Sokoloff had examined its physiological action very thoroughly, and his description gives a good picture of the various stages of an action characteristic of the digitalis series. According to Sokoloff the preliminary stage of vagus inhibition gives way to a very great rise of blood-pressure, due to powerful and very rapid heart-beat and intense vaso-constriction, the action ending in sudden heart-failure. An examination by H. C. Wood, Jun., in 1900, added but little to Sokoloff's description; he rightly, however, ascribed to direct peripheral

action the vaso-constriction which Sokoloff had attributed chiefly to action on the vaso-motor centre. Wood also made the important observation that the commercial crystalline apocynin was almost devoid of activity, and that an apocynin which he prepared himself, though active when first prepared, became less and less so with successive purifications by recrystallization.

Meanwhile some revival of interest in the clinical use of the drug had occurred. A communication on its use made by Woodhull in 1897 produced quite a crop of reports from physicians, who claimed priority in, or independent discovery of its use, or were interested on one side or the other in the controversy concerning its value. Prominent among these was Dabney, who appears to have learned of the drug independently from native sources, and was so convinced of its efficacy that he asserted, in his own words, "an absolute confidence in my ability to entirely discard the use of the trocar whenever a tincture, fluid extract, or infusion of the bark of the root of the genuine *Apocynum cannabinum* can be obtained." Dabney introduced a new element of confusion and uncertainty into the subject by his insistence on the necessity of insuring that the drug was of this one species. In his own words: "Manufacturing chemists, through ignorance, carelessness, or greed, have foisted upon the profession a number of radically different drugs under the name of *Apocynum cannabinum*; hence results obtained by different physicians using different medicines under a common name varied so widely that the drug was eventually discarded altogether. The *Apocynum androsæmifolium*, an utterly worthless weed, is frequently substituted for the *Apocynum cannabinum*, which it closely resembles in appearance." There does not seem to have been any experimental justification for this conclusion; on the other hand, it obviously furnished an enthusiastic advocate with a ready means of explaining away any untoward or unsuccessful result reported with apocynum, as having been due to failure to obtain the right species.

Our object in entering at this somewhat tedious length into the chequered history of this drug is to furnish an adequate explanation for its anomalous position at the present day. When we find the drug vaunted by some as an unfailing specific diuretic in dropsy, being, according to one writer, even in hydrocephalus, "the only remedy on which we can depend"; by others admitted as a remedy, but regarded as "a mere evacuant of dropsical effusions . . . possessing this value in common with jalap and other hydragogue cathartics"; by others, again, admitted to have a digitalis action, but discarded on account of its

emetic and cathartic properties; recommended as a diaphoretic and expectorant, a tonic and alterative, as a remedy for intestinal worms, as a cure for mild cases of intermittent fever, and even as a local application and internal remedy for rattlesnake bite: when we read, on the one hand, that one species alone is active, and yet find the United States Pharmacopœia admitting others under its official definition of apocynum, it is hardly surprising that the great reputation which the drug has enjoyed locally and at times has not crossed the Atlantic. Nevertheless, it would be a matter for regret if these uncertainties and contradictions should lead to the final disuse of a drug in favour of which there is such an accumulation of testimony, even if one may suspect that this is tinged with enthusiasm. Nothing could be more conducive to a juster appreciation of such a drug than a thorough chemical examination, leading to the identification of its active principle. It was particularly fortunate, from one point of view, that it attracted almost simultaneously the attention of the Pharmaceutical Department at Guy's Hospital and of the Wellcome Chemical Research Laboratories, and that while Mr. Finnemore was investigating *Apocynum cannabinum* at the former, Dr. Moore was at work in the latter on a quantity of the drug which was botanically identified as being *Apocynum androsæmifolium*. Mr. Finnemore isolated the substance which has been for some years obtainable as apocynin, identified it as acetovanillone, and confirmed his identification by synthesis. Dr. Moore has obtained the same substance from *Apocynum androsæmifolium* together with its glucoside, which has proved to be no more active than the acetovanillone itself. Finnemore and Moore each isolated also from the species which he examined a crystalline neutral principle, not glucosidal in nature, this principle being found in each case by one of us to have a very powerful action of the digitalis type. So far a good deal of uncertainty was removed. The suggested inactivity of *Apocynum androsæmifolium*, at least as regards this most characteristic action, was shown to be wholly mythical, and we had the opportunity of investigating the action of a crystalline principle, obtained without difficulty in a state of chemical purity, instead of extracts of unknown, probably varying, and certainly not uncomplicated action. It should be mentioned that there is no certainty as yet, from the chemical point of view, that the substances obtained by Finnemore and Moore are the same, though there is every likelihood of their being so. They were named differently and formulated differently by their discoverers:—



We found, however, at an early stage of our respective investigations that we were dealing with substances which were at least physiologically indistinguishable. We therefore joined forces and finished the investigation together. Without taking part in a chemical discussion, which is not our concern, we cannot adopt one name or the other; but we have used Finnemore's cynotoxin and Moore's apocynamarin with absolute indifference, so that, apart from the labels on our records, we should not know which was employed in any particular experiment. The action is very similar to that of the other members of the digitalis group. If the substance enters the circulation slowly, as by hypodermic injection, or, still more so, by absorption from the stomach, there is an initial stage of very marked retardation of the heart-beat by vagus inhibition. In a cat with a normal heart-rate of about 200 per minute, to which a dose of 2 mg. was given by the mouth twice daily for eight days, the beat was kept down to an average rate of about 140 per minute, sinking to 110 per minute, or even lower, in the periods up to three hours after each administration during which the animal might be considered to be under the full effect of the dose. Vomiting occurred only once during this period, and was clearly not due to irritation of the gastric mucous membrane, for the stomach of the animal, which was killed after the experiment was complete, was perfectly normal. When fully under the drug the animal exhibited distinct drowsiness, an effect which some observers have attributed to extracts of apocynum. It is, of course, difficult to be certain of the genuineness of this effect. An animal of nocturnal habit, like the cat, so readily falls into a drowsy condition in the daytime, when left undisturbed in conditions of warmth and comfort, that it is almost impossible to recognize a mildly sedative as distinguished from a definitely narcotic effect. Comparison with other animals, however, and with the same animal in the intervals during which the action of the drug had weakened, inclined us to the conclusion that such a sedative action was actually present. If so, the point may be of practical service in the treatment of heart disease, where the breakdown in compensation is associated with restlessness and insomnia. During the whole of this experiment the cat remained in good condition, ate readily, and put on weight rapidly. In fig. 1 the rates of the heart-beat during the experiment are plotted. It should be noted that the omission of the second dose on one day (the third) was followed by recovery of the heart-beat to near its original rate on the following morning; also that after the last administration the effect of the drug rapidly passed off. There is no evidence, therefore, of

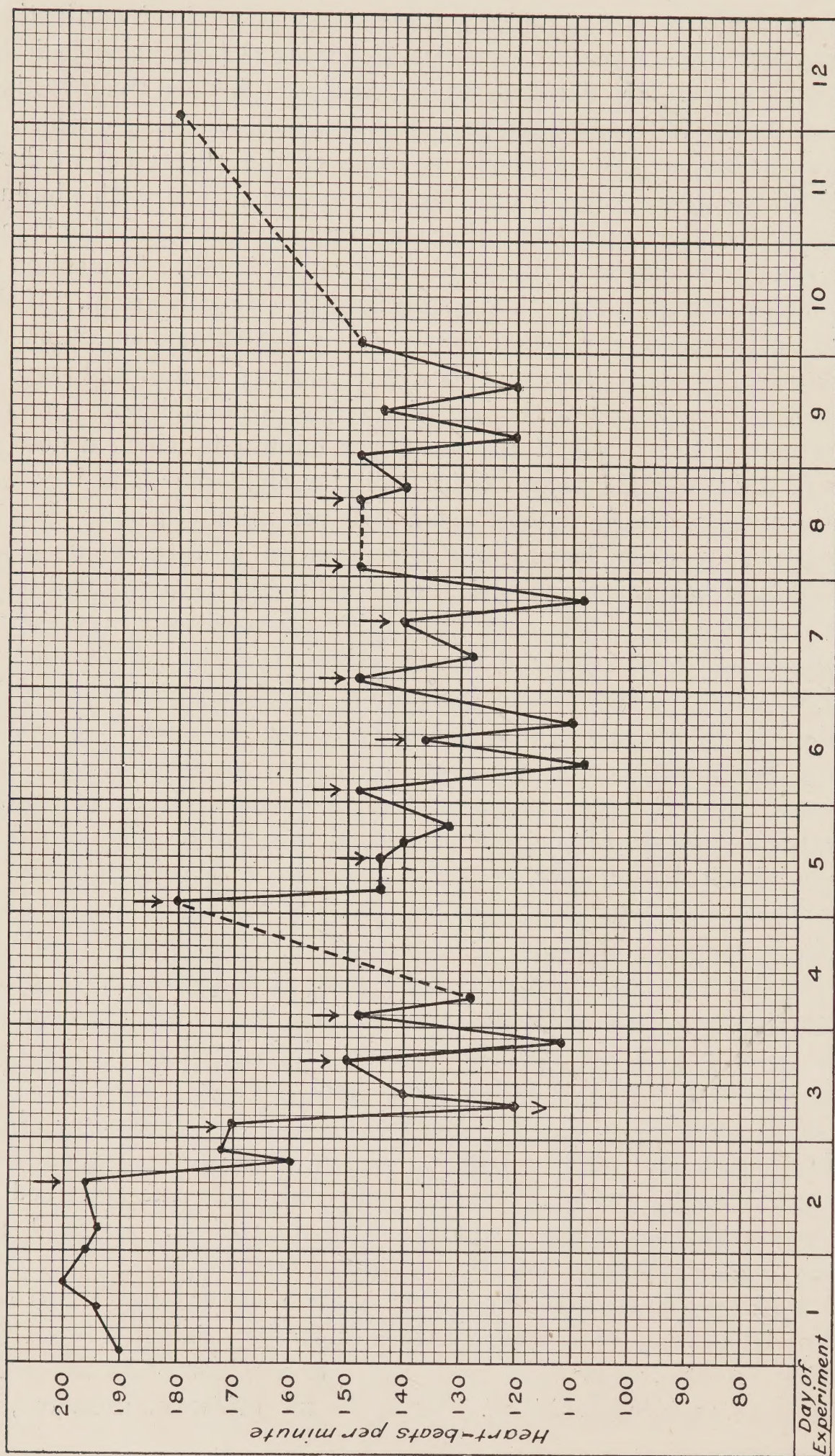


FIG. 1.
Experiment on Cat. ↓ = Administration of 2 mg. apocynamarin by the mouth; v = vomiting.

anything like cumulative effect with this rate and method of administration.

The effects on the heart-beat are illustrated in a more acute form by subcutaneous injection of a small dose. Fig. 2 shows the result of injecting 1 mg. hypodermically into a cat. It will be seen that the rate

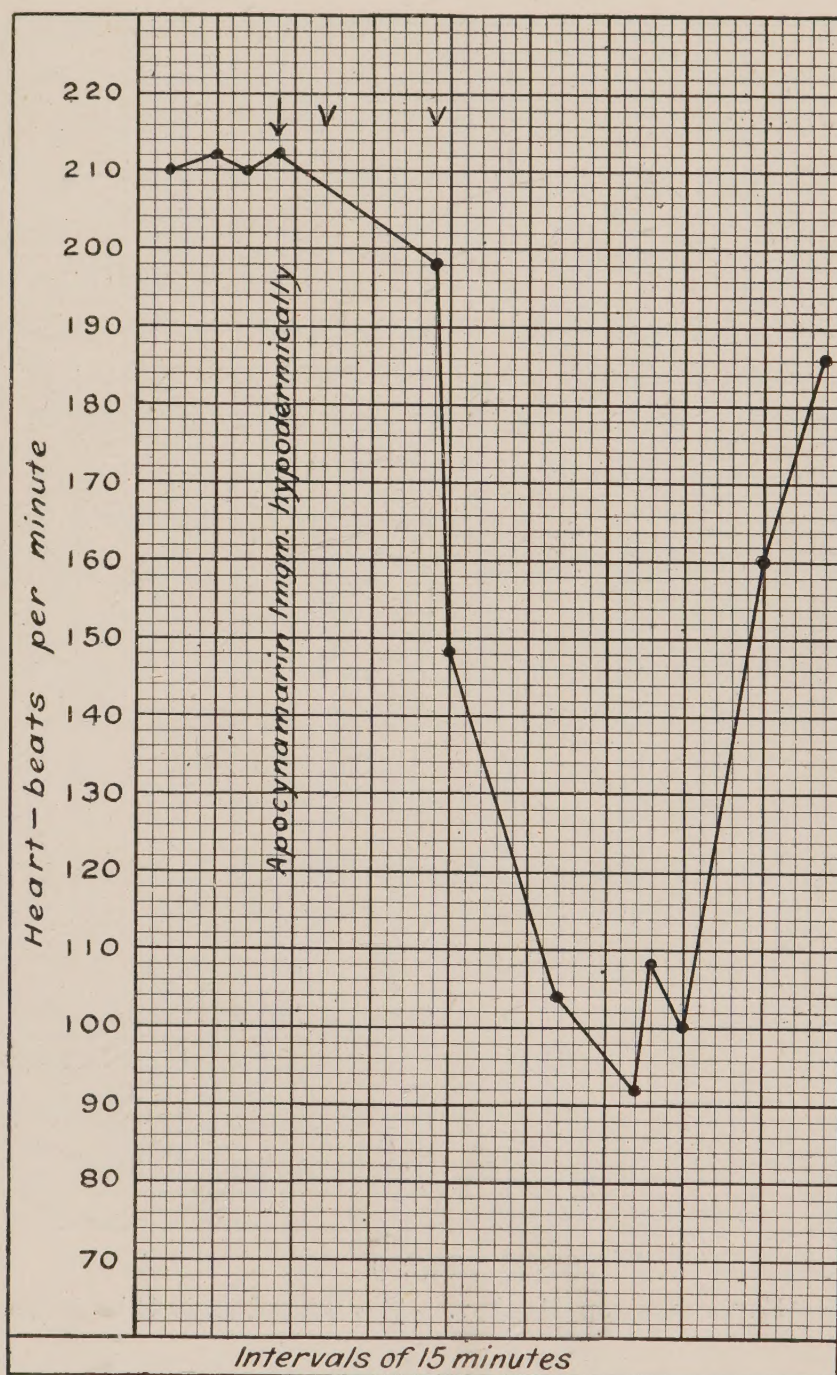


FIG. 2.

Experiment on Cat. ↓ = Hypodermic injection; V = vomiting.

of the heart-beat falls rapidly, and the stage of excessive inhibition, with irregular interruptions of the heart-beat, is soon reached. Recovery is equally rapid, and the whole effect is practically over in one hour. It

should be noted that vomiting is readily caused by this method of administration—a further indication that this effect is not the result of gastric irritation, but must be attributed to the action of the drug, after absorption, either on the vomiting centre or directly on the musculature of the stomach.

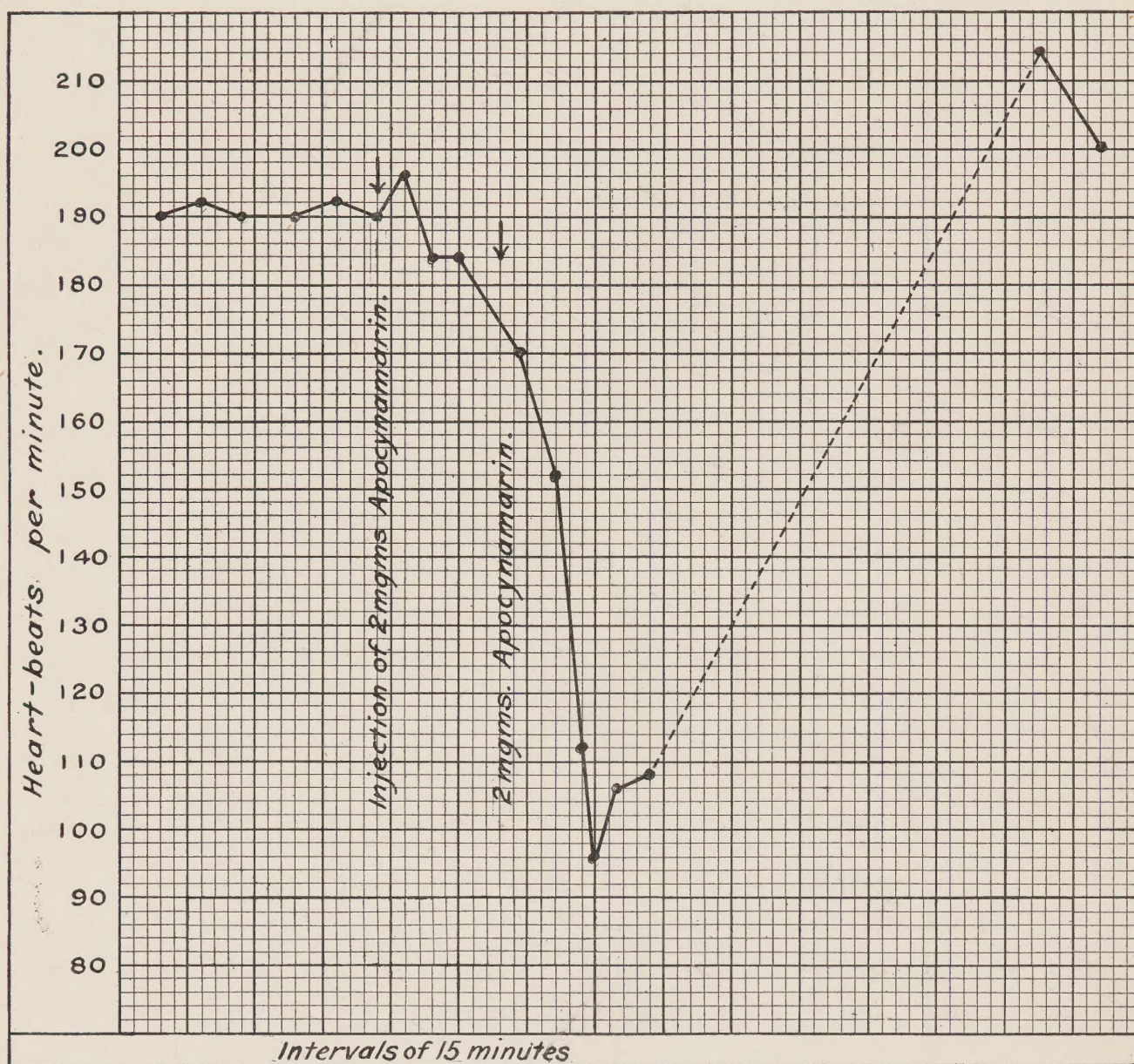


FIG. 3.

Experiment on Monkey. ↓ = Hypodermic injection.

Fig. 3 illustrates the action on the pulse of a monkey. An excessive vagus inhibition occurs as before. In this case, however, the third stage of digitalis action—escape from vagus inhibition, with very rapid pulse—is produced in typical form. From this, however, the animal recovered after a few hours. The effects of the drug can be analyzed more closely by mechanical records of its action on the arteries, heart, and viscera of

the anæsthetized animal, or on isolated organs. It is then seen to have a powerful action on the heart, comparable to that of *strophanthus*, combined with the peripheral excitation of marked tonus in plain muscular organs, including the arteries, the spleen, the uterus, the alimentary canal, and the urinary bladder. On voluntary muscle it has no action. (Tracings illustrating these actions were exhibited by the epidiascope.)

In its action as a diuretic we have not found that apocynamarin (or cynotoxin) occupies an exceptional position in the digitalis series. As others have found with other drugs of this group, the diuresis, accompanied by expansion of the kidney, is much more easy to demonstrate on the rabbit than on the cat or dog. In the latter animals the first effect of an intravenous injection is to cause diminution of the kidney volume and diminished diuresis; this gives way to a secondary expansion of the organ and acceleration of the flow of urine as the blood-pressure falls. The diuresis is best obtained in the cat by injecting the drug hypodermically and allowing it to be absorbed slowly. One then obtains during the earlier stage of the action, in which the rise of blood-pressure due to vaso-constriction is held in check by vagus inhibition, a quite notable increase in the rate of the diuresis. This is a fact which is hard to reconcile with the generally received idea that the diuresis produced by digitalis and its allies is due to increased cardiac activity, for we have here a case of vaso-constriction accompanied by diminished heart-output per unit period sufficient to prevent the rise of arterial pressure which the vaso-constriction would otherwise produce; nevertheless, there is diuresis. On the other hand, perfusion and other experiments have shown that the renal arteries are not immune to the general vaso-constrictor action of these drugs.

It may be suggested that two factors are concerned: (1) A relative insensitiveness of the renal arterioles, leading to a redistribution of the blood in the arterial system of such a kind that more flows through the kidney at the expense of other organs even when the general arterial pressure remains constant; and (2) a fall of venous pressure, owing to accumulation of blood on the arterial side: the renal veins, being near the heart, would be especially affected. These combined influences will lead to increased rate of circulation through the kidney, even, as Loewi has shown, when the organ is prevented from expanding by embedding it in a mass of plaster of Paris. Another point, which is worth attention in this connexion, is the apparent association in the digitalis series of a powerful action on the peripheral arteries with diuretic action.

Thus the two substances which seem to have the most powerful vaso-constrictor action among the members of this series—squill and apocynum—have also a special reputation as potent diuretics. Whether this is to be taken as indicating an actual bio-chemical affinity between the plain-muscle cell and the renal epithelium, so that the latter is directly irritated by substances which excite the former to tonus, is a point on which we are not prepared to offer evidence. It is possible that the diversion of blood to the kidney owing to the prevalence of vaso-constriction in other organs, as above suggested, is adequate to account for this association between vaso-constrictor and diuretic action. It is dangerous also to lay too much stress on the clinical reputation of a drug; it must not be forgotten that digitalis itself ranked as a specific diuretic before its action on the heart was appreciated.

Whatever be the explanation of the diuresis produced in the normal animal, there is not much room for doubt that a principal factor in the restoration of this function, in cases of anasarca of cardiac origin, is the strengthening and regulation of the heart-beat itself, with the consequent relief of the venous engorgement. One other observation which we made incidentally is worth mention, though neither original nor unexpected. The diuretic effect obtained in the rabbit by injecting apocynamarin (or cynotoxin) is very much greater if the injection is made subsequent to a previous dose of one of the purin diuretics (such as caffeine, or theophylline), the visible effect of which has ceased. A similar result was obtained by Jonescu and Loewi, who found that in the dog, after strophanthin, a pronounced diuresis was produced by a dose of caffeine too small to have any such effect when given by itself. The general vaso-constriction and improvement of the heart-beat induced by strophanthin, or the local effect of the caffeine on the kidney, while independently inadequate to produce a sufficient diversion of the blood-stream through the kidney to evoke a perceptible diuresis, acting together became efficient. This reinforcement of digitalis diuresis by xanthin-base diuresis is not new to practical medicine, but the laboratory demonstration of it was so striking as to lead us to investigate the possibility that some other constituent of apocynum might have such a reinforcing effect on the diuretic effect of apocynamarin. We have found no evidence for any such action, and our present view is that the whole activity of the drug in this respect is represented by this active principle. If this view be correct, apocynum must be removed from the exceptional position allotted to it by some clinical advocates and be placed alongside the other members of the digitalis series. It is

satisfactory, on the other hand, to think that the isolation of the pure principle will at length enable it to be tried clinically without any lingering doubts as to the correctness of the species employed or the activity of the preparation. From some points of view we believe it should have advantage over some members of the series. In our experiments on administration by the mouth the effect on the heart was rapidly attained, and could be maintained without any sign of tolerance on the one hand or cumulation on the other. The comparative ease of isolation and purification and the stability of the active principle is another point which should undoubtedly be in its favour, when one considers the difficulty of obtaining in commerce the active principles of digitalis and strophanthus in anything approaching uniformity. On the other hand, the cathartic action of apocynum will probably not be obtained with the pure principle. This, however, we are disposed to regard as an advantage, for some other cathartic can be given if desirable, while it is well not to be hampered or limited in administering a cardiac tonic by its concomitant action on the alimentary canal.

The other diuretic action to which we propose to refer is that of extracts from the infundibular lobe of the pituitary body. The action of extracts of this organ in producing a rise of blood-pressure was discovered by Oliver and Schäfer in 1894. Howell showed that the action was limited to the posterior lobe, developmentally related to the central nervous system. The analogy to the active principle of the suprarenal gland, limited to the medulla, which in development is related to the sympathetic system, was clear, and was indicated by Schäfer and Herring. The latter observers, in amplification of an observation by Schäfer and Magnus, studied the marked diuretic action of the extract and concluded that this was produced by a specific renal excitant, quite distinct from the principle acting on the blood-pressure.

In examining the action of the extract on various organs and tissues, we found that it had a general action on plain muscle very similar to that of certain members of the digitalis series. This action has no apparent relation to innervation by any division of the autonomic system; arteries such as the pulmonary and coronary branches, which receive little or no vaso-motor nerve supply, are stimulated to constriction equally with those governed by sympathetic nerves; the uterus of the cat, which relaxes in the non-pregnant condition and contracts when pregnant, in response to sympathetic nerve impulses or suprarenal extract, contracts in any condition in response to infundibular extract. Similarly, with other plain muscular organs and systems, the response

to the pituitary principle is invariably contraction. This action is not affected by ergotoxin, which eliminates the motor action of sympathetic nerves or suprarenal preparations. So far, then, the pharmacological affinities of this extract are with the digitalis series. Like the digitalis drugs, again, it has practically no action on voluntary muscle. On cardiac muscle its action is comparatively slight. It produces a strengthening of the beat, accompanied by some degree of retardation, but the effects are small. Nothing comparable to the excessive excitation and final systolic rigor produced by the digitalis drugs is seen. If the experiment is made on a heart perfused under constant pressure the initial augmentation of the beat gives way to a secondary weakening. This, however, is doubtless partly attributable to the constriction of the coronary arterioles. In the entire animal, when this constriction is antagonized by the great general rise of systolic pressure, the augmentation of the heart-beat, accompanied by retardation, persists for a long time.

This similarity in its action on the circulatory system to the digitalis group suggested a closer examination of the evidence which led Schäfer and Herring to attribute the diuretic effect to a separate principle. This may be classed under two headings:—

(1) The dissociation of the pressor effect from the diuretic effect in time-relations and relative prominence.

(2) The alleged selective destruction of the pressor principle by certain enzymes and chemical agents.

The dissociation in time-relations of the two actions is seen to be similar to that with which we are familiar in the case of the digitalis drugs. The rise of blood-pressure is attended by initial retardation or cessation of diuresis, followed by increased diuresis, which attains its maximum after that of the arterial pressure, and lasts long after the pressure has returned to the normal. A closely similar sequence may be observed, as we have shown, with apocynamarin or strophanthin, which certainly do not contain separate pressor and diuretic principles. The fact that a second injection will frequently produce a weaker but distinct renewal of diuretic action, without producing an obvious rise of blood-pressure, is also conceivable on the view that one principle produces both effects. The blood-pressure effect is more complex: a heart-depressant principle exists alongside the pressor principle in the extract, and the action of this becomes more significant as the pressor effect becomes weaker with repeated injections. It may be doubted, also, whether effects can be properly compared which depend for their recognition on methods of

such different sensitiveness as the manometric record of blood-pressure and the drop record of diuresis. We have observed cases in which contraction of the uterus was produced by a second injection, which caused practically no rise of blood-pressure; but this would not justify the conclusion that the principle acting on the plain muscle of the uterus is distinct from that which causes vaso-constriction.

We have not been able to find any evidence for a selective destruction of one action or the other by ferments. In our experience both actions are equally unaffected by pepsin, equally readily destroyed by trypsin, and both slowly destroyed at about the same rate by oxidation with hydrogen peroxide. We are disposed, therefore, to regard the evidence brought forward in favour of the existence of two principles as inadequate.

It appears to us that the evidence points to the diuretic action of pituitary extracts as being of a similar type to that produced by the digitalis group of drugs. In the case of pituitary extract, again, the association of vaso-constrictor action, in this case accompanied by but slight action on the heart, with a powerful diuretic action is very marked. It is worthy of mention that we have observed with large doses the production of renal hæmorrhage, as some have recorded after large doses of squill.

